JAMA | Review

Progress and Challenges in Bacterial Meningitis
A Review

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IMPORTANCE Bacterial meningitis is a worldwide health problem, with incidence rates ranging from approximately 0.9 per 100 000 individuals per year in high-income countries to 80 per 100 000 individuals per year in low-income countries. In low-income countries, bacterial meningitis has a mortality rate of up to 54%. Up to 24% of those who survive develop chronic neurological sequelae, such as hearing loss or focal neurological deficits.

OBSERVATIONS *Streptococcus pneumoniae* causes about 72% and *Neisseria meningitidis* causes about 11% of cases of bacterial meningitis in people older than 16 years. *Escherichia coli* and *Streptococcus agalactiae* cause about 35% of cases of early-onset neonatal meningitis. In adults, risk factors for bacterial meningitis include older age and immunosuppressive conditions. The most common symptoms are headache (84%), fever (74%), stiff neck (74%), altered mental status (median [IQR] Glasgow Coma Scale score of 11 [9-14] on a scale ranging from 3-15), and nausea (62%). Brain imaging should be performed before lumbar puncture if patients present with altered mental status, focal neurological deficits, papilledema, or history of immunocompromising conditions or central nervous system disease. Bacterial meningitis should be suspected if any of the following are present on admission: serum leukocytes greater than 10.0 $\times 10^9$/L, cerebrospinal fluid (CSF) leukocytes greater than 2000/μL, CSF granulocytes greater than 1180/μL, CSF protein greater than 2.2 g/L, CSF glucose less than 34.23 mg/dL, or fever. A positive Gram stain result for bacteria is diagnostic, but the sensitivity of a positive Gram stain result for bacterial meningitis ranges from 50% to 90%. In countries in which the prevalence of ceftriaxone-resistant *Streptococcus pneumoniae* exceeds 1%, vancomycin and ceftriaxone are the empirical antibiotics of choice, with the addition of ampicillin in neonates, older patients, and immunocompromised patients. Adjunctive dexamethasone should be used in patients with bacterial meningitis but stopped if *Listeria monocytogenes* is confirmed.

CONCLUSIONS AND RELEVANCE Bacterial meningitis affects approximately 0.9 per 100 000 individuals to 80 per 100 000 individuals per year and has a mortality rate as high as 54%. First-line therapy is prompt empirical intravenous antibiotic therapy and adjunctive dexamethasone.

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JAMA Patient Page page 2170

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Bacterial meningitis causes approximately 318 000 deaths annually worldwide, resulting in an estimated 20 383 years of life lost.[1,2] The incidence ranges from approximately 0.9 per 100 000 individuals per year in high-income countries to approximately 10 to 80 per 100 000 individuals per year in low-income and middle-income countries.[1-3] Mortality rates in adults and neonates with bacterial meningitis range from 6% to 54%. Mortality also varies from 10% in high-income countries to up to 58% in low-income countries. The risks of neurological sequelae, such as focal neurological deficits (eg, hemiparesis, cranial neuropathies), hearing loss, and memory impairment, also vary, from 9.4% in Europe to 25% in Africa.[1-3]

In the US, bacterial meningitis accounts for approximately 13% of all cases of meningitis and encephalitis in adults.[4,5] In people older than 16 years with bacterial meningitis, *Streptococcus pneumoniae* causes 72% of all cases and *Neisseria meningitidis* causes 11% of all cases.[1-3] The overall prognosis of bacterial meningitis has recently significantly improved in high-income countries, most likely due to the use of adjunctive dexamethasone.[6,7] For example, between 2 periods (1998-2002 and 2006-2018) in the Netherlands, the in-hospital mortality rate for pneumococcal meningitis decreased from 31% to 17%.[7] This review summarizes current evidence on the epidemiology, diagnosis, and treatment of bacterial meningitis (**Box**).

Methods

I searched PubMed for English-language articles published from June 1, 2018, through October 4, 2022. I used the term "bacterial meningitis" and found 3469 publications. I also selected commonly referenced and highly quoted older references identified in guidelines and previous review articles. Of 3501 articles identified, 60 were

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Box. Commonly Asked Questions About Bacterial Meningitis

What patients with bacterial meningitis should receive dexamethasone?

Adult patients treated for bacterial meningitis with intravenous antibiotics should receive empirical dexamethasone, because dexamethasone combined with intravenous antibiotics is associated with better outcomes than intravenous antibiotics alone. However, if *Listeria* is confirmed as a pathogen, dexamethasone should be discontinued because dexamethasone is associated with increased mortality in patients treated for *Listeria* meningitis.

How are bacterial meningitis and viral meningitis distinguished on results of a lumbar puncture?

Both bacterial meningitis and viral meningitis are associated with elevated protein and leukocyte counts on spinal fluid. Viral meningitis, but not bacterial meningitis, is typically associated with elevated granulocytes in spinal fluid. Bacterial meningitis should be suspected vs viral meningitis if any of the following variables are present: serum leukocytes greater than 10.0 $\times 10^9$/L, cerebrospinal fluid (CSF) leukocytes greater than 2000/μL, CSF granulocytes greater than 1180/μL, CSF protein greater than 2.2 g/L, CSF glucose less than 34.23 mg/dL, or fever.

How is group B streptococcal neonatal meningitis prevented?

Intravenous penicillin during labor prevents early-onset group B streptococcal neonatal meningitis in pregnant patients with vaginal or rectal colonization with group B streptococcus. Therefore, pregnant patients should be screened for the presence of group B streptococcus with a vaginal and rectal swab during the third trimester, and those who test positive should be treated during labor and delivery with intravenous penicillin.

included, consisting of 39 observational studies, 10 meta-analyses, 7 review articles, and 4 guidelines.

Discussion

Increased rates of vaccination for the most common meningeal pathogens have decreased the incidence of bacterial meningitis. For example, in the US, the introduction of the pneumococcal vaccine in 2000 and the quadrivalent meningococcal vaccine (A, C, Y, and and W135) in 2005 were associated with a decreased incidence of meningitis due to *S pneumoniae* and *N meningitidis*.[3,8] Despite this, *S pneumoniae* and *N meningitidis* remain the most common etiologies of bacterial meningitis.[8,9] In the largest prospective study to date of 1412 adults and children with bacterial meningitis in the Netherlands between 2006 and 2014, the most common pathogens were *S pneumoniae* (72%) and *N meningitidis* (11%).[10]

In neonates, *Streptococcus agalactiae* (ie, group B streptococcus [GBS]), *Escherichia coli*, and *Listeria monocytogenes* are the most common causes of bacterial meningitis.[1-3,11] GBS meningitis is categorized as either early-onset disease (diagnosed between birth and 6 days of age) or late-onset disease (diagnosed between 7 and 89 days of age).[12] GBS bacterial meningitis can be prevented with nonvaccine interventions.[1-3,12] Up to 40% of pregnant patients are colonized in the rectum or vaginal tract with GBS, and vaginal or rectal colonization is the leading cause of neonatal exposure. The Centers for Disease Control and Prevention recommends performing rectal and vaginal cultures at approximately 36 to 37 weeks of pregnancy to detect GBS colonization. Patients with colonization should receive intravenous penicillin G during labor and delivery, which reduces early-onset, but not late-onset, GBS disease (Box).[12] Although intravenous penicillin G can prevent early-onset GBS meningitis in neonates, infections still occur due to false-negative screening results, preterm delivery, and extremely rapid deliveries. Therefore, efforts to develop a GBS vaccine are underway. The most advanced potential vaccine is in phase 2 clinical trials and is a conjugate vaccine that includes 6 serotypes (Ia, Ib, II, III, IV, and V) that cause approximately 98% of GBS meningitis.[12] An effective vaccine would induce maternal immunity with IgG that crosses the placenta, passively transferring immunity to the infants to protect against early- and late-onset disease.[1,12]

Listeria monocytogenes is a food-borne pathogen associated with consumption of contaminated coleslaw, raw vegetables, milk, cheese, contaminated turkey franks, alfalfa tablets, cantaloupe, diced celery, hog head cheese, and processed meats. *Listeria monocytogenes* can cause gastroenteritis, bacteremia, meningitis, or maternal-neonatal infection.[11] *Listeria monocytogenes* causes approximately 1% of bacterial meningitis in neonates and approximately 5% of bacterial meningitis in patients older than 16 years. Most cases of bacterial meningitis due to *Listeria monocytogenes* occur in people older than 50 years or in those with cellular immunodeficiency.[1-3] The intestinal tract is the usual portal of entry.[11] In addition to contaminated food, *Listeria* has been isolated from dust, soil, water, sewage, and decaying vegetable matter (including animal feed and silage). *Listeria* is uncommon in countries with regulated food hygiene safety requirements.[1-3,11]

Clinical Presentation

The classic triad of fever, stiff neck, and a change in mental status occurs only in approximately 41% of patients with acute bacterial meningitis,[10] but is more common in patients older than 60 years.[1] In a study of 696 patients with bacterial meningitis, the triad of fever, stiff neck, and mental status change occurred in 58% of 257 patients 60 years and older and 36% of 439 patients younger than 60 years.[1,10] In a study of 1412 people with bacterial meningitis, the most common presenting symptoms were headache (84%), fever (74%), stiff neck (74%), altered mental status (median Glasgow Coma Scale score of 11; scale range, 3-15), and nausea (62%).[10] Patients may also present with aphasia or hemiparesis or monoparesis (22%), coma (13%), cranial nerve palsy (9%), and rash (8%). Concomitant infections typically include sinusitis or otitis (34%), pneumonia (9%), and endocarditis (1%).[10]

Cranial Imaging in Patients With Symptoms or Signs of Meningitis

Obtaining a computed tomography (CT) image of the brain before a lumbar puncture is common clinical practice to evaluate for intracranial abnormalities that could potentially place patients at risk for herniation during a lumbar puncture.[1-3] A prospective study of 301 adults with suspected meningitis identified that an abnormal head CT imaging result was associated with the following characteristics: immunocompromised state, history of central nervous system (CNS) disease such as brain tumor or strokes, new-onset seizure, papilledema, reduced level of consciousness, and focal neurological deficit.[13] In 2004, the Infectious Diseases Society of America (IDSA) guidelines recommended that only patients with these

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characteristics should undergo brain imaging prior to a lumbar puncture when bacterial meningitis is suspected.[14] To evaluate adherence to IDSA guidelines, an observational study conducted between 2005 and 2010 of 614 adults with meningitis showed that clinicians ordered cranial imaging in 549 patients (91%).[15] In 356 of these patients (65%) there was no clinical indication for imaging per IDSA guidelines, and only 2 (0.5%) had minor intracranial findings that did not prompt a change in treatment.[15] Furthermore, a head CT scan with normal findings does not exclude the possibility of complications in bacterial meningitis. Up to 40% of 43 patients with bacterial meningitis whose health deteriorated after undergoing the lumbar puncture had normal findings on brain imaging tests.[16] To expedite optimal medical care, brain imaging should not be performed in patients without a clinical indication and empirical antibiotic therapy should not be withheld while awaiting results of a brain imaging test. The UK, European, and Swedish guidelines have more strict indications for brain imaging in patients with bacterial meningitis, which include lower (worse) Glasgow Coma Scale scores (eg, <10 or <12), new-onset seizures, papilledema, or history of a CNS disease as indications to perform a CT scan and do not consider a history of immunosuppression (eg, solid organ or bone marrow transplant recipient, long-term steroid recipient, or HIV infection) as an indication for cranial imaging. Adherence to some of these guidelines in clinical practice is suboptimal. For example, in a study of 1326 episodes of bacterial meningitis, 604 of 900 patients (67%) without a clinical indication still underwent cranial imaging.[16-19] A study of 202 adults with bacterial meningitis showed that all the guidelines correctly identified patients with cerebral herniation, but only the IDSA guidelines did not miss any major intracranial findings or findings that prompted a neurosurgical intervention.[20]

Early detection of bacterial meningitis is important because bacterial meningitis can be associated with mortality in up to 54% of patients and neurological complications can occur in up to 25% of patients. Approximately 50% of patients with bacterial meningitis present within 24 hours of developing symptoms such as fever, severe headache, stiff neck, nausea, vomiting, and altered mental status.[10] Approximately 50% of patients with meningococcal meningitis present with petechial or purpuric rash and disseminated intravascular coagulation.[1-3] Delays in diagnosis and administration of antibiotic therapy are associated with increased mortality. For example, mortality rates are as high as 45% when antibiotics are administered more than 6 hours after presentation, compared with mortality rates of 4% to 6% in patients in whom antibiotic therapy is started promptly.[21] A clinical trial of 301 adults with bacterial meningitis randomized patients to receive adjunctive dexamethasone vs placebo in addition to standard intravenous antibiotics. The trial demonstrated a reduction in unfavorable outcomes (mortality or neurological sequelae) in those who received the adjunctive steroids; this benefit was primarily due to a greater response in the subgroup of patients with pneumococcal meningitis (52% in the placebo group vs 26% in the dexamethasone group; relative risk, 0.50 [95% CI, 0.24-0.83]; $P < .001$).[1] Delays in diagnosis and therapy can occur when brain imaging occurs prior to lumbar puncture or in patients without meningeal signs, such as neck stiffness, or in older patients with atypical presentations.[22] In a retrospective study of 123 patients with bacterial meningitis, obtaining a brain imaging study before a lumbar puncture was associated with a delay of more than 6 hours in antibiotic therapy initiation.[21] However, obtaining a brain imaging study before lumbar puncture was not associated with a delay of more than 6 hours in antibiotic initiation in a prospective study of 203 adults with suspected meningitis.[16]

Physicians have typically used the presence of meningeal signs (neck stiffness and Kernig and Brudzinski signs) to help identify patients who should undergo lumbar puncture and empirical therapy for bacterial meningitis.[1-3] Tests such as the Kernig and Brudzinski signs to identify meningismus, defined as symptoms of stiff neck due to meningeal inflammation, were originally developed and tested in patients with severe, late-stage bacterial meningitis and in meningitis caused by tuberculosis. The Brudzinski sign consists of spontaneous flexion of the hips during passive flexion of the neck. The Kernig sign is defined by the inability or reluctance to allow full extension of the knee when the hip is flexed 90° while the patient is in the supine position. The original descriptions of the meningeal signs showed excellent sensitivities, but the studies were done in patients with untreated bacterial and tuberculous meningitis.[23] Currently the diagnostic accuracy of meningeal signs in adults with suspected meningitis is poor, with sensitivities ranging from 5% for both Kernig and Brudzinki signs to 30% for nuchal rigidity, defined as inability to flex the neck.[23] A late diagnosis, defined as diagnosis and treatment of meningitis only after admission to the hospital, occurs in approximately one-third of patients with bacterial meningitis and is more common in patients without the classic meningitis triad, in older patients, and in those with concomitant pneumonia. A late diagnosis is associated with delays in initiation of antibiotic therapy, lower rates of adjunctive steroids administration, and increased mortality, from 18% to 36%.[22]

Differentiating Between Bacterial and Aseptic Meningitis

In 1925, Wallgren defined aseptic meningitis as an acute community-acquired syndrome with a cerebrospinal fluid (CSF) white blood cell count more than 5 cells/μL with a negative CSF Gram stain and culture, without a parameningeal focus or systemic illness and with no mortality or neurological sequelae.[3] Aseptic meningitis causes approximately 72% of cases of meningitis in adults and children, while bacterial and fungal meningitis cause approximately 8% each of the rest of cases. Currently, aseptic meningitis is most commonly caused by viruses such as Enteroviruses, West Nile virus, and Herpes simplex virus type 2, but can also be caused by several other infectious and noninfectious etiologies, such as drug-induced, meningeal carcinomatosis, and autoimmune disorders. The typical CSF profile in bacterial meningitis shows a white blood cell count usually more than 1000/μL, neutrophilic pleocytosis (>50% neutrophils on the CSF white blood cell differential), an elevated protein (usually >100 mg/dL), and hypoglycorrhachia (<30 mg/dL) in the majority of patients.[1-3] A CSF white blood cell count less than 5 cells/μL can be seen in up to 2% of patients with bacterial meningitis.[24] A Gram stain and culture should be performed in all adults and children presenting with meningitis irrespective of the CSF white blood cell count. The sensitivity of the CSF Gram stain is approximately 50% to 90% in adults with bacterial meningitis.[10,20] Furthermore, approximately 95% of all adults presenting with meningitis have a negative Gram stain result, creating diagnostic and treatment challenges to clinicians.[25] Only 8% of adults presenting with meningitis have bacterial meningitis, but most receive empirical antibiotic

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therapy.[25] Clinical models have been derived and validated that can aid clinicians in distinguishing between aseptic and bacterial meningitis. In children, the bacterial meningitis score (range, 0-6) uses the following weighted variables to identify bacterial meningitis: a positive Gram stain result (2 points), a CSF protein value greater than 80 mg/dL (1 point), a blood absolute neutrophil count greater than 10 000 cells/μL (1 point), seizures (1 point), and a CSF neutrophil count greater than 1000 cells/μL (1 point). A score of greater than or equal to 2 points suggests bacterial meningitis[26] and has a sensitivity of 99.3%, specificity of 62.1%, and negative predictive value of 99.7%. In this scoring system, a positive Gram stain result indicates the presence of bacterial meningitis when the patient's presentation is consistent with bacterial meningitis.[26] A risk score was derived and validated in 960 adults with meningitis and a negative Gram stain.[27] In this study, the following variables were associated with an acute treatable infection (eg, bacterial meningitis, herpes simplex encephalitis, fungal etiology): immunosuppression, age older than 60 years, abnormal neurological examination findings, CSF glucose value less than 45 mg/dL, CSF protein greater than 100 mg/dL, and serum white blood cell count greater than 12 000 cells/μL.[27] Patients who had none of these variables had zero risk of having an urgent treatable cause for their meningitis.[27] The score was further validated in 214 patients with culture-proven bacterial meningitis who presented with a negative Gram stain result with 100% sensitivity.[27] An additional risk score was recently derived and validated in adults that helped differentiate confirmed viral CNS infections from patients with bacterial meningitis who presented with a negative Gram stain.[28] This model included the following variables: serum leukocytes greater than 10.0 $\times 10^9$/L, CSF leukocytes greater than 2000/μL, CSF granulocytes greater than 1180/μL, protein greater than 2.2 g/L, glucose less than 34.23 mg/dL, and fever on admission. Patients with none of the risk scores were at "low risk" of having bacterial meningitis with 99.5% to 100% sensitivity. Despite the availability of risk scores that identify patients at low risk of bacterial meningitis, most adults and children with viral meningitis continue to receive empirical antibiotic therapy for 3 days while awaiting cultures, which increases their length of stay and thus exposes them to unnecessary antibiotic therapy and increasing costs.[4,5] The purpose of these clinical models is to stratify the risk of bacterial meningitis in patients presenting to the emergency department. In patients at high risk of having bacterial meningitis, antibiotic therapy should be started promptly and continued while awaiting blood and CSF cultures.

Biomarkers

Biomarkers, such as CSF lactate concentration, may help distinguish bacterial and aseptic meningitis.[29,30] Two meta-analyses of 1692 and 1885 patients reported that CSF lactate was associated with better diagnostic accuracy (area under the curve of 0.98 for CSF lactate vs 0.94 for CSF leukocytes, 0.88 for CSF glucose, and 0.86 for CSF protein) than other characteristics of the CSF, such as white blood cell count, glucose, and protein levels.[29,30] However, in patients who received antimicrobial therapy before lumbar puncture, the sensitivity of CSF lactate was only approximately 49%.[30] Several proteins, such as the C-reactive protein, and procalcitonin may help discriminate between bacterial and viral meningitis.[31,32] A recent meta-analysis of 2058 patients reported a sensitivity of 95% and a specificity of 97% for serum procalcitonin with an excellent diagnostic accuracy of serum procalcitonin (area under the curve of 0.98).[32] Other potential biomarkers that could help with diagnostic testing for bacterial meningitis include CSF concentrations of cortisol, heparin-binding protein, soluble triggering receptor expressed on myeloid cells 1 (TREM-1), interleukins (IL-6, IL-12, IL-1β, TNF), and complement levels, but validation studies are needed.[1]

Polymerase Chain Reaction

Antibiotic therapy is administered empirically for most adults and children with meningitis despite that the most common causes are viruses. Antibiotic therapy can decrease the sensitivity of the CSF Gram stain and culture creating uncertainty in the etiological diagnosis.[33,34] The UK guidelines in 2016 recommended obtaining a polymerase chain reaction (PCR) test for the most common viral and bacterial etiologies (Enterovirus, Herpes simplex virus, Varicella zoster virus, *S pneumoniae*, and *N meningitidis*) in patients presenting with meningitis.[17] In 2015, a multiplex polymerase chain reaction panel approved by the US Food and Drug Administration rapidly identified 14 etiologies in 1 hour, but in clinical practice approximately 2.9 hours is required to obtain results from a multiplex polymerase chain reaction.[35]

In a 2022 meta-analysis of 19 studies, the multiplex PCR showed a sensitivity of 89.5% and a specificity of 97.4% for bacterial isolates and a sensitivity of approximately 75.5% to 93.8% and a specificity of 99% for viral pathogens.[36] The multiplex PCR was associated with a lower rate of antimicrobial therapy and shorter length of stay in patients with confirmed viral infections.[37] Novel diagnostic and surveillance tools that are currently undergoing evaluation are next generation metagenomic sequencing, and laboratory detection of resistant mutations that could improve the diagnosis and therapy of bacterial meningitis.[38,39]

Empirical Antibiotic Therapy

Empirical antibiotic therapy should be started promptly when a patient presents with possible bacterial meningitis and continued if the CSF profile is suggestive of bacterial meningitis (**Table 1**). A delay in administering antimicrobial therapy of more than 6 hours is associated with increased mortality, from 6% to 45%, and with increased rates of neurological sequelae, from 10% to 70%.[21,40] In countries in which the prevalence of ceftriaxone resistance *S pneumoniae* is more than 1% (defined as a minimum inhibitory concentration ≥2 mg/L), vancomycin should empirically be added to ceftriaxone pending susceptibility results.[1-3,17,18] *Listeria monocytogenes* should be empirically treated with intravenous ampicillin in patients who are immunosuppressed and in neonates and patients older than 50 years.[1-3] Despite poor CSF penetration, gentamicin should be considered in combination with penicillin because this combination of therapy was associated with reduced mortality in a recent large observational study.[1] Trimethoprim-sulfamethoxazole can be used in patients with suspected neurolisteriosis with allergy to penicillin.[14,16-18] Antimicrobial therapy should be modified once the pathogen is identified and susceptibility testing is available (**Table 2**). If the CSF multiplex PCR panel result is positive for a viral pathogen or if the patient is at low risk for having bacterial meningitis, antibiotic therapy may be discontinued if no other clear indications exist, such as sepsis.

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Table 1. Empirical Antibiotic Therapy for Suspected Bacterial Meningitis

Age or predisposing condition	Suspected pathogens[a]	Antibiotic therapy[b]	Intravenous (IV) antibiotic dosing for adults with normal kidney function
Neonate (<1 mo)	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin plus cefotaxime or gentamicin	Vancomycin: 15 to 20 mg/kg IV every 8 to 12 h (not to exceed 2 g per dose or a total daily dose of 60 mg/kg)
1-23 mo	*Streptococcus agalactiae*, *Escherichia coli*, *Streptococcus pneumoniae*, *Neisseria meningitidis*	Vancomycin plus cefotaxime or ceftriaxone	Ceftriaxone: 2 g IV every 12 h
2-50 y	*Streptococcus pneumoniae*, *Neisseria meningitidis*	Vancomycin plus cefotaxime or ceftriaxone	Cefotaxime: 2 g IV every 4 to 6 h
>50 y	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*	Vancomycin plus cefotaxime or ceftriaxone plus ampicillin	Ampicillin: 2 g IV every 4 h
Immunosuppression[c]	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Salmonella* species	Vancomycin plus cefotaxime or ceftriaxone plus ampicillin	Aztreonam: 2 g IV every 4 or 6 h

[a] Listed in order of the most common pathogens.

[b] Cefotaxime or ceftriaxone alone is appropriate in countries where the prevalence of cephalosporin-resistant pneumococcus is less than 1%.

[c] Immunosuppression includes AIDS, solid organ or bone marrow transplant, and long-term steroid prescriptions.

Prognosis

Mortality in bacterial meningitis varies by pathogen and country. For example, mortality rates in adults ranged from 6% in Germany to 54% in Malawi.[42,43] In neonates, mortality varies from 10% in high-income countries to 58% in low-income countries.[44,45] Similarly, neurological and neurocognitive sequelae, such as hearing loss, focal neurological deficits, or memory impairment, vary by geography from 9.4% in Europe to up to 21% and 25% in Southeast Asia and Africa, respectively.[44] The risk of neurological sequelae varies by pathogen (*N meningitidis*, 7.2%; *Haemophilus influenzae* type B, 9.5%; *S pneumoniae*, 24.7%).[46] A total of 9 risk scores have been developed to identify patients at higher risk of death and/or neurological sequelae in patients with bacterial meningitis, pneumococcal meningitis, or invasive meningococcal disease.[47-56] Risk factors for adverse clinical outcomes include older age, hypotension, seizures, no antibiotics prior to hospital admission, concomitant pneumonia, purpuric rash, tachycardia, lower score on the Glasgow Coma Scale, focal neurological deficits, a CSF white blood cell count of less than 1000 cells/μL, a positive blood culture result, and a high serum C-reactive protein concentration.[47-56] None of the scores had adequate diagnostic accuracy to be recommended for routine use in individual patient treatment.[47]

Dexamethasone

Dexamethasone reduces inflammation in the CSF caused by bacteriolytic antibiotics, such as third-generation cephalosporins and vancomycin, and can improve clinical outcomes in bacterial meningitis.[1-3] A meta-analysis of 25 randomized clinical trials involving 4121 participants (2511 children and 1517 adults; 93 studies that included both adults and children) evaluated the association of adjunctive steroids with improved outcomes in patients with bacterial meningitis. The meta-analysis included 9 studies from low-income countries and 16 from high-income countries.[57] Corticosteroids were associated with reduced mortality in *S pneumoniae* meningitis, but not in *H influenzae* or *N meningitidis* meningitis in adults. Corticosteroids were associated with lower rates of severe hearing loss in children with *H influenzae* meningitis (relative risk, 0.34 [95% CI, 0.20-0.59]) but not in children with meningitis due to non-*Haemophilus* species. Corticosteroids were associated with reduced hearing loss (relative risk, 0.58 [95% CI, 0.45-73]) and with lower rates of short-term neurological sequelae (relative risk, 0.64 [95% CI, 0.48-0.85]) in high-income countries. Corticosteroid therapy was not associated with improved outcomes in low-income countries. Adjunctive dexamethasone, 10 mg, intravenously every 6 hours for 4 days have been recommended by international guidelines since 2004 in adults and should be administered within 20 minutes of the first dose of antibiotic.[14,16-19] Administration of adjunctive dexamethasone in the Netherlands in an observational trial reduced mortality by 10% in 357 adults with pneumococcal meningitis.[58] In the US, adjunctive steroids are used only in approximately one-third of patients with pneumococcal meningitis and are associated with lower rates of mortality.[4] In an observational study of 1391 patients, steroids were associated with lower rates of unfavorable outcomes in bacterial meningitis caused by nonpneumococcal meningitis with the exception of *Listeria monocytogenes*.[59] In a nationwide observational study of 252 patients from France with neurolisteriosis, adjunctive dexamethasone was associated with higher rates of mortality (absolute rates not provided; odds ratio, 4.58 [95% CI, 1.50-13.98]; $P = .008$).[41] However, randomized clinical trials are needed to more rigorously assess this association. In children in high-income countries, adjunctive dexamethasone is associated with lower rates of hearing loss in *H influenzae* meningitis from approximately 11.9% to 3.9%. The introduction of conjugate vaccines reduced rates of hearing loss after *H influenzae* meningitis.[1-3,12] Steroids have not shown benefit in children with bacterial meningitis due to pathogens other than *H influenzae*. Therefore, only approximately 8% of infants and children with CNS infections receive adjunctive steroids.[5] The IDSA guidelines recommend that intravenous dexamethasone in a dose of 0.15 mg/kg every 6 hours should be given to adults before the first dose of antibiotics, based on a clinical trial of 301 patients that showed a reduction in unfavorable outcomes (death or neurological disability) from 52% in the placebo group to 26% in the dexamethasone group in patients with pneumococcal meningitis ($P = .006$).[14] The European and UK guidelines recommend steroid administration within 4 and 12 hours after the first dose of antibiotic.[1,17] Adjunctive dexamethasone should be discontinued

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Table 2. Antibiotic Therapy for Bacterial Meningitis Based on Pathogen

Pathogens	Preferred[a]	Alternative	Common antibiotic adverse events (rate, %)	Additional considerations
Haemophilus influenzae			Penicillin rash (1-10); gastrointestinal adverse effects (10)	May cause seizures in patients with kidney failure
β-lactamase negative	Ampicillin	Ceftriaxone, cefotaxime, cefepime, or fluoroquinolones (levofloxacin or ciprofloxacin or moxifloxacin)	Ampicillin diarrhea (4.5); rash/hives (3.4)	Cross reactivity to other β lactams occurs in patients allergic to penicillin
β-lactamase positive	Ceftriaxone or cefotaxime	Cefepime, or fluoroquinolones (levofloxacin, ciprofloxacin, or moxifloxacin)	Ceftriaxone or cefotaxime: transaminitis (3.1); diarrhea (2.7); rash (1.7)	Cross reactivity to other β lactams occurs in patients allergic to penicillin
Neisseria meningitidis			Cefepime rash (4); diarrhea (3); nausea (2)	May cause of encephalopathy
Penicillin MIC <0.1 ìg/mL	Penicillin G or ampicillin	Ceftriaxone, cefotaxime	Ceftaroline diarrhea (8-10); nausea/vomiting (3-5)	Only cephalosporin with methicillin-resistant *Staphylococcus aureus* activity
Penicillin MIC 0.1-1.0 ìg/mL	Ceftriaxone or cefotaxime	Fluoroquinolones (levofloxacin, moxifloxacin, or ciprofloxacin) or meropenem	Fluoroquinolones gastrointestinal (up to 20); tendinitis (2)	Can prolong QT corrected for heart rate interval, so check baseline electrocardiogram
Streptococcus pneumoniae			Meropenem diarrhea (2.5); rash (1.4); nausea (1.2)	Seizure risk much lower than imipenem/cilastatin (<1% vs 3%-33%)
Penicillin MIC ≤0.06 ìg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime	Vancomycin nephrotoxicity (up to 18); red man syndrome (2)	Adjust dose to achieve vancomycin serum trough concentrations of 15 to 20 µg/mL
Penicillin MIC ≥0.12 ìg/mL	Ceftriaxone or cefotaxime	Meropenem or cefepime	Daptomycin diarrhea (5.2); rash (4.3); elevated creatine phosphokinase (2.8)	Not active in pneumonia; discontinue daptomycin if creatine phosphokinase >1000 U/L if myositis symptoms are present
Ceftriaxone or cefotaxime MIC <1.0 ìg/mL	Ceftriaxone or cefotaxime	Meropenem or cefepime	Linezolid diarrhea (4.3); nausea (3.4); headache (2.2)	If used for >2 wk, up to one-third of patients can develop reversible myelosuppression
Ceftriaxone or cefotaxime MIC ≥1.0 ìg/mL	Vancomycin plus ceftriaxone or cefotaxime	Vancomycin plus fluoroquinolones (moxifloxacin or levofloxacin)	Trimethoprim-sulfamethoxazole gastrointestinal (3-8); rash (3-4); acute kidney injury (5.8)	Excellent cerebrospinal fluid penetration
Enterobacteriaceae	Ceftriaxone or cefotaxime	Aztreonam, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), trimethoprim-sulfamethoxazole, meropenem, or ampicillin		
Listeria monocytogenes	Ampicillin or penicillin G plus gentamicin	Trimethoprim-sulfamethoxazole		
Streptococcus agalactiae	Ampicillin or penicillin G	Ceftriaxone, cefotaxime, or vancomycin		
Staphylococcus aureus				
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin, linezolid, or daptomycin		
Methicillin-resistant	Vancomycin	Trimethoprim-sulfamethoxazole, linezolid, daptomycin, or ceftaroline		

Abbreviation: MIC, minimal inhibitory concentration.

[a] Dosing for adults with normal kidney function: vancomycin: 15 to 20 mg/kg intravenous (IV) every 8 to 12 hours (not to exceed 2 g per dose or a total daily dose of 60 mg/kg); ceftriaxone: 2 g IV every 12 hours; cefotaxime: 2 g IV every 4 to 6 hours; penicillin G: 4 million units IV every 4 hours; ampicillin: 2 g IV every 4 hours; aztreonam: 2 g IV every 4 or 6 hours; ciprofloxacin: 400 mg IV every 8 to 12 hours; gentamicin: 1.7 mg/kg every 8 hours with dosage and interval individualized by obtaining a target peak gentamicin level of 7-9 mg/L and a trough level of 1-2 mg/L; meropenem: 2 g IV every 8 hours; moxifloxacin: 400 mg IV every 24 hours; nafcillin: 2 g IV every 4 hours; oxacillin: 2 g IV every 4 hours; trimethoprim-sulfamethoxazole: 5 mg/kg every 8 hours based on the trimethoprim component.

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immediately if meningitis is due to *Listeria monocytogenes* because steroids are not beneficial in these patients and have adverse effects.[60] Steroids did not reduce mortality for bacterial meningitis in low-income countries, most likely because patients are sicker on presentation. In patients presenting early with symptoms of bacterial meningitis, dexamethasone could be beneficial in low-income countries.[58]

Vaccination for Bacterial Meningitis

Over the past approximately 40 years, conjugate vaccines for *H influenzae* type b, *N meningitidis*, and *S pneumoniae* have significantly decreased the incidence of meningitis due to these pathogens.[1-3,8] Conjugate vaccines consist of the pathogen's polysaccharide antigen bound to a carrier protein that stimulates T cell–dependent processing of the antigen. The conjugate vaccines reduce mucosal colonization by bacteria, thereby enhancing herd immunity, and produce better T-cell immunity than polysaccharide vaccines that do not bind the polysaccharide antigen to a carrier protein.[1-3] The efficacy of these vaccines can be hampered by the emergence or persistence of bacterial serotypes that are not included on the vaccine.[3,8] For example, the conjugate meningococcal group A vaccine that was introduced in sub-Saharan Africa in 2013 virtually eliminated group A serotype outbreaks, but epidemics with meningococcal serogroup W, X, and C and nonmeningococcal pathogens continue to occur.[44]

Limitations

This review has several limitations. First, quality of included evidence was not evaluated. Second, relevant studies may have been missed. Third, some recommendations of this article, such as the utility of cranial imaging or the use of adjunctive dexamethasone, may not be generalizable to resource-limited settings where access to clinical care is suboptimal. Fourth, the review focused on the medical management of bacterial meningitis and did not address the neurocritical care aspects such as external ventricular drains or intracranial pressure monitoring.

Conclusions

Bacterial meningitis affects from 0.9 per 100 000 individuals per years in high-income countries to 80 per 100 000 individuals per year in low-income countries, with mortality rate as high as 54% and neurological sequelae rate as high as 24% in low-income countries. First-line therapy is prompt empirical intravenous antibiotic therapy and adjunctive dexamethasone in adults.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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